PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P837PC00	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DK 03/00940	International filing date *(day/month/year)* 30.12.2003	Priority date *(day/month/year)* 02.01.2003
International Patent Classification (IPC) or both national classification and IPC A61K39/395		
Applicant PEDERSEN MEDICAL A/S et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26.07.2004	15.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Herrero, M Telephone No. +49 89 2399-8542

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00940

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-26 as originally filed

Claims, Numbers

1-30 received on 24.02.2005 with letter of 22.02.2005

Drawings, Sheets

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☒ the claims, Nos.: 27, 28, 30, 33, 34
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 30 with respect to industrial applicability

   because:

   ☒ the said international application, or the said claims Nos. 30 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-30
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-30
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-29
	No:	Claims	

2. Citations and explanations

see separate sheet

SECTION I

6. Additional observations

6.1 The amended Claims 1-30 filed with the letter dated 22.02.05 have their basis in the originally filed application, and therefore satisfy Article 34(2)(b) PCT.

6.2 The present preliminary examination report has been established taking into account the observations concerning novelty and inventive step of the subject-matter encompassed by the newly filed Claims 1-30 set forth in the Applicants' letter of 22.02.05.

SECTION III

Claim 30 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT (i.e. methods of treatment of the human or animal body by therapy). Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

SECTION V

2. CITATIONS AND EXPLANATIONS

2.1 The following documents have been considered for the purposes of this report:

D1: US-A-4734279 (also cited in the application)
D2: EP-A-1068871 (also cited in the application)
D3: Dolgushin, I.I. et al (1997) ZH Mikrobiol. Epidemiol. Immunobiol. 4:111-115
D4: GB-A-2229725
D5: FR-A-2573627
D6: Baenziger, J. et al (1974) J. Biol. Chem. **249**:1889-1896
D7: WPI/Derwent Abstract of JP 2000 270858

2.2 The application discloses what in the light of the available prior art appears to be a novel and non-obvious type of antimicrobial composition comprising lysozyme and immunoglobulins which is effective i.a. against Gram negative bacteria, and suitable for local use on mucosal membranes and/or skin (Art. 33(2) and (3) PCT).

The essential feature which distinguishes the present antimicrobial compositions pertains to the use of glycosylated immunoglobulins which have been synthetically prepared by being dissolved in a solution comprising disaccharide or monosaccharide. This characterizing feature, which results from the hereby performed additional glycosylation of native (glycosylated) immunoglobulins is neither anticipated nor suggested by the available prior art documents (cf D1, D2, D3, D4 or D5).

The antimicrobial composition of interest characterized in the experimental part of the description comprises lysozyme and glycosylated immunoglobulins directed against antigens on the surface of Gram negative bacteria (cf page 8, lines 26-28; page 11, lines 9-13), wherein said glycosylated immunoglobulins are prepared by dissolving native immunoglobulins in a solution of glucose and incubating for a predetermined period of time to allow the formation of covalent bonds between the glucose and the Fc fragment of the subject immunoglobulins (cf page 9, lines 19-28; sentence bridging pages 21-22). By glycosylating the Fc fragment according to this approach the ability of the processed immunoglobulins to agglutinate is unchanged, while their resistance against both pancreatic and bacterial proteases is highly increased (cf page 10, lines 15-16) .

The resulting antimicrobial composition, which comprises agglutinating glycosylated antibodies against the type of Gram negative bacteria intended to be treated, apparently solves the problem of lysozyme penetrating the outer lipopolysaccharide membrane of said Gram negative bacteria, thus creating a possibility of degrading the peptidoglycan membrane resulting in bacteriolysis (cf. page 8, lines 21-35 bridging over page 9, lines 1-2; Examples 1-2).

In line with the above, the antimicrobial compositions according to Claims 1-26, the

method for their production defined in Claim 27 and the intended (medical) applications of said compositions according to Claims 28-30 would appear to satisfy the novelty and inventive step requirements of Arts. 33(2) and (3) PCT.

2.4 Industrial applicability (Art. 33(4) PCT)

For the assessment of the present Claim 30 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2.5 Further comments

(i) The application as originally filed contains no technical information concerning the performance of antimicrobial compositions of the type pursued in present Claims 20-21, in which the lysozyme is conjugated to a monosaccharide (e.g. mannose). The subject-matter of Claims 20-21 would therefore appear to lack support (within the meaning of Art. 6 PCT) and disclosure (within the terms of Art. 5 PCT) vis-à-vis the description and drawings.

(ii) Claims 12-15 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. By simply referring to desirable properties of the glycosylated immunoglobulins which form part of the antimicrobial compositions of interest said claims attempt to define the pursued compositions in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

(iii) With respect to Claims 12-14 and 27 it is noted that the use of expressions like "such as" or "optionally" (or "for example" or "preferably"...) has no limiting effect on the scope of said claim, i.e. the feature(s) following such expressions is(are) to be

regarded as entirely optional (cf PCT Guidelines, C-III, 4.6).

Claims

1. Antimicrobial composition comprising ~~a system of~~ lysozyme and glycosylated immunoglobulins, wherein said glycosylated immunoglobulins have been produced by being dissolved in a solution comprising disaccharide or monosaccharide.

2. Antimicrobial composition according to claim 1 for local use on mucosal membranes and/or skin.

3. Antimicrobial composition according to claim 1, wherein said glycosylated immunoglobulins have affinity to Gram negative bacteria.

4. Antimicrobial composition according to claim 3, wherein the Gram negative bacteria are rods and/or cocci or a combination thereof.

5. Antimicrobial composition according to claim 1, wherein said glycosylated immunoglobulins have affinity to Gram positive bacteria.

6. Antimicrobial composition according to claim 1, wherein said glycosylated immunoglobulins have affinity to viruses.

7. Antimicrobial composition according to claim 3, wherein the glycosylated immunoglobulins have affinity to antigen determinants on the cell wall of Gram negative bacteria.

8. Antimicrobial composition according to claim 1, wherein the glycosylated immunoglobulins are of monoclonal or polyclonal origin.

9. Antimicrobial composition according to claim 1, wherein the glycosylated immunoglobulins are of monoclonal and/or polyclonal origin or a combination thereof.

10. Antimicrobial composition according to claim 1, wherein the glycosylated immunoglobulins are of the classes IgM, IgG, IgY, IgA or dimer IgA.

11. Antimicrobial composition according to claim 1, wherein the glycosylated immunoglobulins are of the IgG class and/or the IgY class.

12. Antimicrobial composition according to any of the preceding claims, wherein the glycosylated immunoglobulins are intact and/or resistant to proteases such as bacterial proteases and/or pancreatic proteases.

13. Antimicrobial composition according to any of the claims 1 to 11, wherein the glycosylated immunoglobulins are intact and/or resistant to proteolytic enzymes such as papain and/or bromelain and/or pepsin.

14. Antimicrobial composition according to any of the claims 1 to 11, wherein the glycosylated immunoglobulins are intact and/or resistant to acidic conditions such as in gastric juice.

15. Antimicrobial composition according to any of the claims 1 to 11, wherein the glycosylated immunoglobulins have lost their ability of complement fixation.

16. Antimicrobial composition according to claim 1, wherein the glycosylated immunoglobulins originate from a biological fluid such as milk, whey, blood, plasma, colostrum, yolk or serum.

17. Antimicrobial composition according to claim 1, wherein the glycosylated immunoglobulins originate from a biological fluid such as milk and/or colostrum and/or yolk and/or a combination thereof.

18. Antimicrobial composition according to claim 1, wherein the glycosylated immunoglobulins originate from immunized animals and/or non-immunized animals.

19. Antimicrobial composition according to claim 1, wherein the lysozyme is native or conjugated.

20. Antimicrobial composition according to claim 19, wherein the lysozyme is conjugated to a monosachharide.

21. Antimicrobial composition according to claim 20, wherein the lysozyme is conjugated to mannose.

22. Antimicrobial composition according to claim 1, wherein the lysozyme is extracted from egg white.

23. Antimicrobial composition according to claim 1, wherein the antimicrobial composition is selected from the groups of a cream, an ointment, a gel, a wet tissue, a tablet to chew, a lozenge and chewing gum.

24. Antimicrobial composition according to claim 1, wherein the antimicrobial composition is in the form of a lozenge or chewing gum.

25. Antimicrobial composition according to claim 1, wherein said lysozyme constitutes in the range of 0.05% to 10% by weight of of the composition.

26. Antimicrobial composition according to claim 1, wherein said glycosylated immunoglobulins constitute in the range of 0.1% to 10% by weight of of the composition.

~~27. Antimicrobial composition, comprising lysozyme conjugated to a monosaccharide.~~

~~28. Antimicrobial composition according to claim 27, comprising lysozyme conjugated to mannose.~~

27. A method for the preparation of the antimicrobial composition according to any of the claims 1-26 comprising the steps of

b) obtaining immunoglobulins
c) glycosylating the immunoglobulins
d) obtaining native or conjugated lysozyme

e) mixing the glycosylated immunoglobulins and the lysozyme, and optionally adding additives, thereby obtaining the antimicrobial composition.

~~28. A method for the preparation of the antimicrobial composition according to any of claims 27 to 28 comprising the steps of~~

~~a) obtaining the lysozyme~~

~~b) conjugating the lysozyme.~~

28. Use of lysozymes and glycosylated immunoglobulins for the preparation of an antimicrobial composition as defined by any of the claims 1-26.

29. Use of lysozymes and glycosylated immunoglobulins for the preparation of an antimicrobial composition as defined by any of the claims 1-26 for the prophylaxis and/or treatment of an infection.

~~33. Use of a conjugated lysozyme for the preparation of an antimicrobial composition as defined by any of the claims 27-28.~~

~~34. Use of a conjugated lysozyme for the preparation of an antimicrobial composition as defined by any of the claims 27-28 for the prophylaxis and/or treatment of an infection.~~

30. A method of preventing and/or treating an infection in an animal, including a human, comprising administering to said animal an effective amount of the composition as defined in any of claims 1-~~28~~ 26.